# NCOHR New Frontier Seed Grant Program 2018
# Report on Research Outcomes and Future Plans

## SEED GRANT PROJECT

**Title**: *TNFα, inflammatory bowel disease, and periodontal disease in the elderly*.
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**Summary of project:**
Inflammatory bowel disease (IBD) is associated with various oral manifestations, and management of these co-morbidities in the elderly poses a significant challenge for oral health care specialists. In this project we addressed whether the increased incidence of periodontal disease (PD) in IBD patients is a biological consequence of the chronic inflammatory IBD condition, or whether it could be the result of decreased oral hygiene adherence due to the oral mucosal manifestations. We approach this question from a foundational as well as all relevant clinical perspectives (Periodontology, Oral Medicine, Dental Hygiene, Gastroenterology).

A biological link between IBD and PD would likely involve systemic circulating pro-inflammatory cytokines such as TNFα, which plays an important role in both diseases. On the other hand, oral manifestations due to IBD might lead to reduced oral hygiene adherence, which by itself could lead to increased incidence of PD. This would provide a mechanism independent of TNFα.

Entry point were results from TNFΔARE mice, a TNF-based model for IBD, that showed lack of periodontal disease at an age when IBD was well-established. We hypothesized that 1) systemic TNFα levels due to IBD are insufficient to periodontal disease. Furthermore, we hypothesized that oral manifestations in IBD patients were associated with reduced oral hygiene causing increased incidence of PD. These two hypothesis were addressed in two independent research objectives (see below)

Establishing whether there is a biological reason for the increased incidence of PD in IBD patients or whether the association is due to decreased oral hygiene adherence would have profound implications: whereas former is more difficult to deal with, particular in the light that anti-TNF therapies are frequently counter-indicated in the elderly, an association involving oral decreased oral hygiene could readily be addressed. If our hypothesis is correct, then oral hygiene consultation should follow any IBD diagnosis.

**Project Aims, Deliverables and Progress:**

**Objective 1:** Establish whether increased TNFα levels are sufficient, predispose, or irrelevant for the induction of alveolar bone loss. For this we characterized the etiology of the oral manifestations in TNFΔARE mice**.**

**Progress**: Male and female TNFΔARE (TNFΔ/WT) and control WT mice were analyzed at two time points (2 months, onset of IBD; 4 months, established severe IBD for changes to

temporomandibular joint (TMJ), buccal mucosa, gingival epithelium, and alveolar bone. In vivo MicroCT (µCT) scans were acquired using Milabs® U-CT scanner and analyzed using Avizo 9.1.1. Oral manifestations were assessed using histology (Hematoxylin & Eosin, TRAP, Safranin O) and immunofluorescence to assess proliferation (Ki67), inflammation (CD45), bone remodeling (SOST, RANKL). 4-months but not 2-months old TNFΔ/WT showed oral manifestations associated with arthritis (TMJ) or Crohn's disease (cobblestone mucosa). No evidence of active periodontal disease was found. 4-months old female mice showed gingival hyperplasia, severe TMJ arthritis, malocclusion and alveolar bone loss (ABL) in the absence of other signs of PD (epithelial inflammation, bleeding). 4-month-old TNFΔ/WT male mice presented TMJ arthritis, cobblestone mucosa, lack of hyperplasia but some limited presence of leukocytes at the gingival epithelium, periodontal ligament, and buccal mucosa. Other signs of PD (epithelial inflammation, bleeding) were also missing.

**Conclusion**: This presents strong evidence that circulating TNFα is not sufficient to induce PD. The role of TNFα in oral tissues is complex. TMJ arthritis and malocclusion might trigger ABL in female TNFΔARE mice in the absence of PD. Sex-specific differences in oral manifestations (hyperplasia vs. cobblestone mucosa) might be directly related to local rather than systemic differences in TNFα.

**Objective 2:** Assess whether incidence and severity of PD in IBD patients stratifies with oral manifestations and/or with oral hygiene adherence.

To address this objective, we performed first a retrospective analysis from data from Kaye Edmonton Clinic patients' electronic health records between the years of 2013 to 2019. A total of 80 patient charts reported IBD or CD or UC in their medical history were included in the study. Data revealed that patients having IBD in the age group 50-64 years were the most affected by PD. These patients also had a more severe form of periodontal disease (Stage III). There was no gender difference. IBD patients with a history of smoking did not show higher odds of developing PD. From this limited study, oral hygiene adherence from the limited data collected in the present study did not affect the severity of periodontal disease in patients presenting with IBD.

**Conclusion**: Age has a significant effect on IBD-affected individuals in developing periodontal disease. Patients above 50 years of age might be followed up more closely for early diagnosis and cure.

**Knowledge translation:**

Results from this project were presented at several national and international conferences:

International Association of Dental Research (IADR General Session 2019, 2021) (poster presentations), American Association for Oral Medicine (AAOM 2021) (oral presentation), American Academy of Oral and Maxillofacial Pathology (AAOMP 2021) (poster presentation).

Publications reporting are currently in preparation.

**Future work:**

The discovery of sex-specific differences in oral manifestations in TNF-mutant mice is currently being followed up with local support from the Funds of Dentistry, School of Dentistry, University

of Alberta. We are also investigating to what degree the increased presence of TNFα in oral tissues affects the oral microbiome, and whether sex-specific differences can be identified.

A prospective clinical study is in preparation.